

Lymphatic abnormalities in Alagille's syndrome

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Abstract

Chylous pleural effusions developed in a patient with Alagille's syndrome who had dysplasia of the lymphatic system. Lymphatic abnormalities are not a recognised feature of Alagille's syndrome.

The features of Alagille's syndrome or arterio-hepatic dysplasia as described by Alagille *et al*^{1,2} and Watson and Miller³ are congenital heart disease (particularly pulmonary artery stenosis), intrahepatic cholestasis, and dysmorphic facies. Other features have been described,⁴ but abnormalities of the lymphatic system have not previously been reported.

Case report

A 19 year old man with Alagille's syndrome was admitted for investigation after a recent deterioration in exercise tolerance. He was born four weeks prematurely, the third child of elderly parents. He failed to thrive and at three months a blowing systolic murmur was noted. There was no history of cyanosis or feeding difficulties. At 6 months, a paediatric cardiologist made a clinical diagnosis of a ventricular septal defect. Cardiac catheterisation was performed when he was 18 months old. It showed an atrioventricular canal defect, equal right and left ventricular pressures, a gradient of 35 mm Hg across the

pulmonary valve, and mild stenosis of the left pulmonary artery.

He achieved normal developmental milestones but height and weight remained below the third centile. At the age of eight the results of cardiac catheterisation were unchanged. At operation (aged 10), cardiomegaly was noted with considerable lymphatic engorgement in the anterior mediastinum, a large multiloculated cystic lesion containing lymph overlying the main pulmonary artery, and serpiginous distended lymphatic vessels surrounding the aorta. A large septum primum defect and cleft mitral valve were repaired. The tricuspid valve had no septal cusp whatsoever and a pulmonary valvotomy was performed.

After operation he remained small and on examination was slightly jaundiced with mild hepatosplenomegaly. When he was 14 he was referred to a paediatric endocrinologist, primarily for investigation of his short stature. He had a prominent forehead, deep set eyes, and a small pointed chin. Blood count and endocrine investigations were normal. The serum concentration of bilirubin was raised but concentrations of other hepatic enzymes were normal. A liver biopsy was not performed because of persistently abnormal clotting. The bone age was delayed by four years and no vertebral anomalies were present. Fundoscopy showed prominent Schwalbe's lines and no retinal pigmentation. The findings of typical facies, congenital heart disease, mildly deranged liver function, and short stature indicated a diagnosis of Alagille's syndrome.

Five years later when he was 19 increasing breathlessness on exertion developed without cyanosis. A chest radiograph (fig 1) showed bilateral pleural effusions and he was admitted for investigation. The liver and spleen were mildly enlarged and there was continued rise of the serum concentration of unconjugated bilirubin. Serum concentrations of cholesterol and triglycerides and lipoprotein electrophoresis were all normal. The prothrombin time was prolonged (18 seconds, control 14 seconds) though the activated partial thromboplastin time, thrombin time, and anti-thrombin III activity were normal.

The pleural effusions were aspirated and found to be chylous. Lymphangiography showed considerable abnormalities of the lymphatic system. The lymphatic vessels in the right foot were very small and could not be cannulated. Lymphatic vessels in the left lower leg seemed normal. In the pelvis there was abnormal cross filling to the right with

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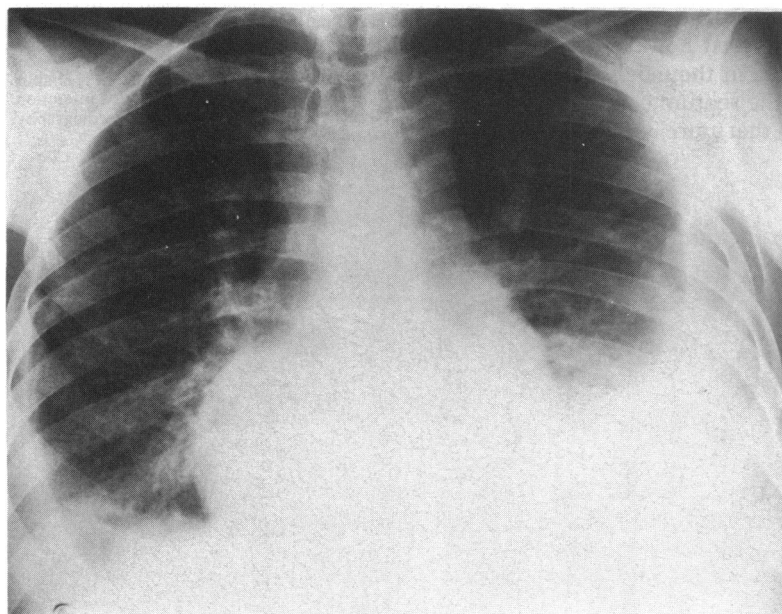


Figure 1 Chest radiograph showing bilateral pleural effusions.

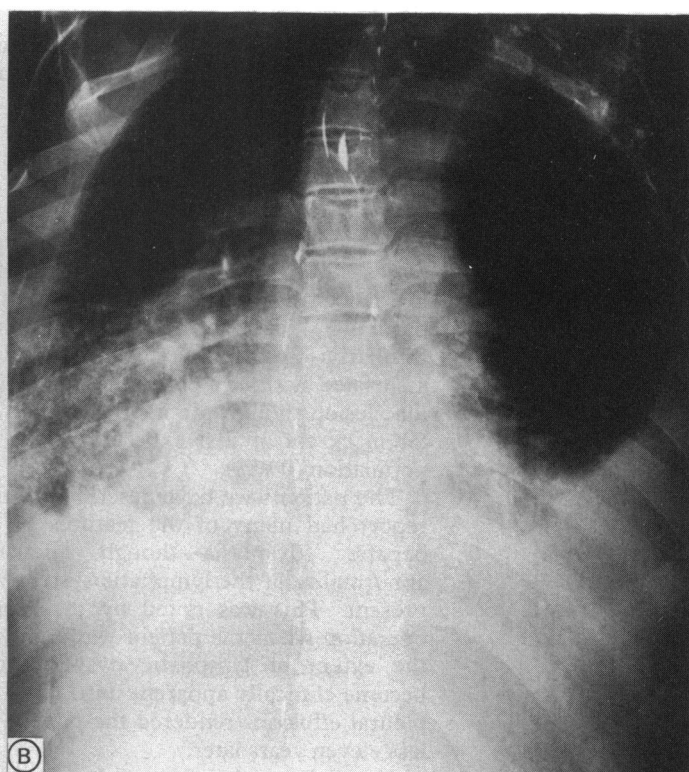
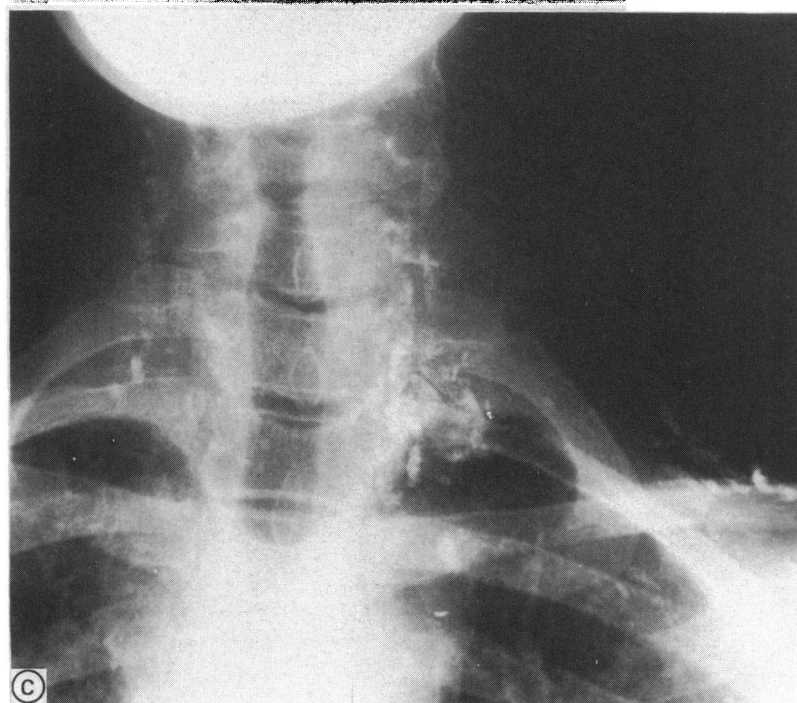


Figure 2 (A) Lymphangiogram film showing cross filling to right pelvic lymphatic vessels with contrast dispersed widely in the lumbar region. (B) Right lateral decubitus chest radiograph after lymphangiography showing pooling of contrast in ectatic lymphatic vessels and absence of the normal thoracic duct. (C) Lymphangiogram film showing contrast in nodes in the neck and left supraclavicular region.



tortuous and ectatic pelvic lymphatic vessels. Contrast was dispersed over a wide area around the lumbar spine (fig 2A). The thoracic duct was not clearly defined and ectatic thoracic lymphatic vessels were found, particularly in the decubitus position (fig 2B). Another unusual feature was filling of lymph

nodes in the neck, left supraclavicular, and axillary regions (fig 2C).

Treatment with a medium chain triglyceride diet was started and the effusions remain unchanged.

Discussion

Alagille's syndrome, or arteriohepatic dysplasia, affects several organ systems but abnormalities of the lymphatic system have not previously been described. The syndrome is probably not rare, because groups of patients as large as nine³ to 15² have been reported. Though the cause remains unknown it seems to be genetic, with autosomal dominant inheritance and variable penetrance being supported by several reports of vertical transmission.⁴

A prominent feature of the syndrome is its clinical variability. Cholestasis may be mild, or absent in later years, with a range of cardiac lesions (though peripheral pulmonary stenosis is the most common). Diagnosis rests on the recognition of a constellation of features including hepatic abnormalities (neonatal jaundice and hypercholesterolaemia with a paucity of intrahepatic ducts) and congenital heart defects (peripheral pulmonary stenosis, pulmonary valve stenosis, and septal defects (both atrial and ventricular). Retinal abnormalities include Schwalbe's lines, Axenfeld's anomaly, and pigmentation. Abnormal vertebrae, impaired renal function suggesting a

tubular defect, hypogonadism, hypothyroidism, absent reflexes, and poor academic performance have also been described.^{5,6} Other syndromes of familial intrahepatic cholestasis may be clearly distinguished by their characteristic biochemical and physical features.

Patients with lymphatic hypoplasia usually present with lymphoedema. Congenital heart disease is rare in these patients (a 1.4% incidence was described in one series⁷) and no particular cardiac lesion predominates. Similarly, lymphatic hyperplasia was not associated with any particular congenital cardiac lesion though the incidence of 9.7% was far in excess of that expected in the general population (0.9%).

The patients we have described in this case report had many of the features of arteriohepatic dysplasia—though considerable abnormality of the lymphatic system was also present. This was noted by the surgeon at operation when the patient was eight, though the extent of lymphatic dysplasia did not become clinically apparent until large chylous pleural effusions rendered the patient breathless eleven years later.

Alagille's syndrome carries a better prog-

nosis than other forms of intrahepatic cholestasis, with most patients surviving into adulthood. The abnormalities are rather more widespread than the name arteriohepatic dysplasia implies and lymphatic dysplasia should perhaps be added to the features of this syndrome.

We thank Dr G K Morris for permission to report this case.

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